PATENT CASE: SF0977XB US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Elizabeth Bates *et al.*	
For Patent: Monocyte-Derived Nucleic Acids and Related Compositions and Methods	Examiner: Chun Crowder Group Art Unit: 1644
Serial No.: 10/780,043	
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DECLARATION UNDER 37 C.F.R. § 1.132 OF JOSEPH H. PHILLIPS

I, Joseph H. Phillips, declare and state as follows:

1. I earned a B.A degree with highest honors in Biology from Williams College in 1975, an M.A. degree with highest honors from Williams College in 1977, and a Ph.D. from the University of Texas in 1983. I was a Graduate Student in Immunology at the University of Texas from 1977-1983 and a postdoctoral Research Fellow at Becton Dickinson Monoclonal Center Inc. from 1983-1985. From 1985 to 1991, I was a Research Scientist at Becton Dickinson Monoclonal Center, Inc. from 1985-1986 and a Senior Research Scientist at Becton Dickinson Immunocytometry Systems, Inc. from 1986-1991. Since 1991, I have been employed at companies affiliated with Schering Corporation, the assignee of the present patent application. At these Schering-affiliated companies, my research has focused primarily on delineating the cell surface

molecules expressed on human leukocytes (particularly NK cells, mast cells and monocytes) that regulated immune interactions. Attached is a copy of my *curriculum vitae* (Exhibit A).

2. I am familiar with the invention of the above-identified application. I am also familiar with the prior art issues raised in the July 17, 206 and November 20, 2006 Office Actions issued in the above-identified application and with the arguments that have been made by Applicants in the Response filed October 10, 2006 in support of patentability of the pending claims.

3. I am aware that in the Office Action dated November 20, 2006, the Examiner has cited Adema et al., publication No. WO 98/24906 ("Adema") as prior art against the pending claims (Office Action p. 4). I am aware that Adema discloses the protein FDF03 (also known as "PILRalpha"), a protein expressed in monocytes. I am also aware that the present application is directed to a homolog of FDF03, and that this homolog is referred to in the application as FDF03-S1 (also known as FDF03act and PILRbeta). I am familiar with the similarities and differences between the sequences and biological activities of these two proteins.

4. I make this Declaration to supplement the submission of data that supports the conclusion that while the FDF03 and FDF03-S1 proteins are very similar, there are significant differences in several regions of the sequences of the two proteins to allow for the production of monoclonal antibodies with specificities for each receptor.

5. The FDF03 family consists of two closely related human genes, FDF03 (PILRalpha) and FDF03-S1 (FDF03act or PILRbeta). Unlike humans and chimps, which contain only two genes, FDF03 and FDF03-S1, the mouse genome contains a second activating gene PILRbeta2 (~85% identical to FDF03-S1) and 6 pseudogenes. FDF03 (PILRa) is a type I membrane protein and member of the immunoglobulin superfamily with a single variable (V) domain, a transmembrane segment and a prominent cytoplasmic tail. The intracellular domain contains a classic ITIM motif as well as a immunoreceptor tyrosine-based switch motif (ITSM). FDF03 is thus an inhibitory receptor that will recruit

phosphatases upon ITIM phosphorylation. FDF03-S1 (FDF03act or PILRb) is highly similar to FDF03 (83% identical) with the N-terminus of the extracellular domain demonstrating the most similarities. Unlike FDF03, FDF03-S1 possesses a transmembrane domain with a charged amino acid and essentially no intracellular domain. FDF03-S1 exclusively pairs with Dap12 and thus is a potent activating receptor when triggered by agonistic antibodies.

6. Although the extracellular domains of FDF03 and FDF03-S1 are very similar, there are significant differences in several regions of the two proteins to allow for the production of monoclonal antibodies with specificities for each receptor. For example, in the human FDF03 protein, there is a region consisting of amino acids 158 thru 165 that is not present in FDF03-S1. Standard monoclonal antibody production technology can allow generation of antibodies that will specifically recognize this region and thus be specific for the FDF03 protein and not the closely related FDF03-S1 protein. Conversely, the extracellular stock region of FDF03-S1 (amino acids 173-187) is significantly different from the stock region of FDF03 and thus monoclonal antibodies specific for this region can be generated that recognize the FDF03-S1 protein only.

7. Since FDF03 and FDF03-S1 are functionally very different receptors, antibodies that specifically recognize these receptors will induce vastly different biologies. For example, antibodies against FDF03 will inhibit mast cell degranulation responses, while antibodies against FDF03-S1 will actually induce mast cell degranulation.

8. Table I summarizes a series of monoclonal antibodies generated by immunizing rats with an FDF03-S1 fusion protein (the extracellular region of mouse FDF03-S1 fused with the Fc of human Ig) or with an FDF03 fusion protein (the extracellular region of mouse FDF03 fused with the Fc of human Ig). The resultant antibodies were tested for reactivity against FDF03 and FDF03-S1. Three types of antibodies were generated by these immunizations:

1. antibodies that recognize both FDF03 and FDF03-S1;
2. antibodies that recognize FDF03 only; and
3. antibodies that recognize FDF03-S1 only.

Table 1

Antibody Name	DX	Isotype	Immunogen	Specificity
MB452-1F11	258	rIgG2a	FDF03-S1 fusion protein	mFDF03-S1 + mFDF03
MB452-2A8	259	rIgG1	FDF03-S1 fusion protein	mFDF03-S1
MB452-3A9	260	rIgG1	FDF03-S1 fusion protein	mFDF03-S1
MB452-3D9	261	rIgG2a	FDF03-S1 fusion protein	mFDF03-S1 + mFDF03
MB452-4B8	173	rIgG1	FDF03-S1 fusion protein	mFDF03-S1 + mFDF03
MB452-4E9	262	rIgG2a	FDF03-S1 fusion protein	mFDF03-S1
MB452-5C3	263	rIgG2a	FDF03-S1 fusion protein	mFDF03-S1
MB452-6D6	264	rIgG1	FDF03-S1 fusion protein	mFDF03-S1 + mFDF03
MB452-8H4	172	rIgG2a	FDF03-S1 fusion protein	mFDF03-S1 + mFDF03
MB452-10E5	171	rIgG2a	FDF03-S1 fusion protein	mFDF03-S1
MB452-11E2	265	rIgG1	FDF03-S1 fusion protein	mFDF03-S1
MB452-11F5	266	rIgG1	FDF03-S1 fusion protein	mFDF03-S1
MB452-13E10	267	rIgG2a	FDF03-S1 fusion protein	mFDF03-S1 + mFDF03
MB765-015	276	rIgG1	FDF03 fusion protein	mFDF03
MB765-027	277	rIgG1	FDF03 fusion protein	mFDF03
MB765-222	278	rIgG1	FDF03 fusion protein	mFDF03
MB765-312	279	rIgG1	FDF03 fusion protein	mFDF03

9. An alternative method for raising antibodies with the desired specificity for FDF03-S1 proteins would be to immunize with known variable regions, such as the extracellular stock region of FDF03-S1 (amino acids 173-187).

10. In view of the above, I am of the opinion that, using standard antibody technology and information available in the current specification about the sequences of FDF03 and FDF03-S1, it is possible to generate antibodies that will specifically recognize FDF03-S1 and not FDF03.

11. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application and any patent issued thereon.

5/17/07
Date

Joseph H. Phillips

CURRICULUM VITAE

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Education:

Ph.D. - University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston, Texas 1983

M.A. - William College, Williamstown, Massachusetts 1977

B.A. - Williams College, Williamstown, Massachusetts 1975

Awards and Honors:

Highest Honors in Biology, Williams College, 1975 and 1977

Sigma XI,1975

Whitehall Foundation Research Fellowship, 1975

Professional Activities:

American Association of Immunologists
Associate Editor, *Journal of Immunology*, 1990-1993
American Association for the Advancement of Science
The New York Academy of Sciences, member.

Experience:

Senior Fellow, Department of Discovery Research/Oncology, Schering-Plough Biopharma, 2005-present.

Principal Staff Scientist, Department of Immunology/Department of Discovery Research, DNAX Research Institute, 2000-2005.

Research Fellow, Department of Immunology, DNAX Research Institute for Molecular and Cellular Biology, Inc., 1991-2000.

Senior Research Scientist, Becton Dickinson Immunocytometry Systems, 1986-1991.

Research Scientist, Becton Dickinson Monoclonal Center, Inc., 1985-1986.

Postdoctoral Research Fellow, Becton Dickinson Monoclonal Center, Inc., 1983-1985.

Graduate Student in Immunology, University of Texas, M.D. Anderson Hospital and Tumor Institute. 1977-1983.

Research Interests:

Research in the ten years has clearly indicated that the immune system functions successfully by maintaining a critical balance between states of activation and inhibition. Understanding the molecules and mechanism through which leukocytes are stimulated, as well as inhibited, will delineate the balance points at which therapeutic manipulation can be directed. The well characterized CD28/CTLA4 system of counterbalanced receptors has presented strong evidence that these regulatory circuits are critical for normal immune functions. Likewise, defects in these receptors can cause profound effects on the immune system resulting in autoimmune and neoplastic pathologies.

My research interest for the last 25 years have focused primarily on delineating the cell surface molecules expressed on human leukocytes (particularly NK cells, Mast cells and monocytes) that regulate immune interactions. These regulatory molecules encompass both stimulatory and inhibitory pathways and clearly play important roles in balancing immune responses. Understanding how these receptors regulate immune responses has allowed us to manipulate the immune environment and begin to actively direct the outcome of immunological reactions during inflammation and cancer.

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